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General

Guideline Title

Clinical practice guideline on systemic lupus erythematosus.

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement

▮▮▮▮▮	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▯▯	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▯	Rating the Strength of Recommendations
▮▮▮▮▮	**Specific and Unambiguous Articulation of Recommendations**
▮▮▮▮▯	**External Review**
▮▮▮▮▮	**Updating**

Recommendations

Major Recommendations

Levels of evidence (1++ to 4 or Ia to IV) and grades of recommendation (A to D, GCP or A to D) are defined at the end of the "Major Recommendations" field.

Diagnosis of Systemic Lupus Erythematosus (SLE)

Early Detection

Prognosis

Do early detection and early treatment improve the prognosis and survival of people with systemic lupus erythematosus?

D - The guideline development group (GDG) does not recommend screening for SLE in the general asymptomatic population.

C - The GDG suggests the early determination of antinuclear (anti-double-strand deoxyribonucleic acid [dsDNA], anti-Ro, anti-La, anti- Sm, anti-ribonucleoprotein [RNP]) and antiphospholipid antibodies in individuals with symptoms that are suggestive of SLE, in order to detect early and less severe forms of the disease.

C - The GDG recommends early treatment with hydroxychloroquine in people with incomplete forms of SLE (understood as those that do not meet the classification criteria), who are carriers of suggestive autoantibodies, to delay the development of the disease and the development of renal impairment.

Suspect Symptoms

What are the main symptoms and signs that should make us suspect systemic lupus erythematosus?

B - The GDG recommends clinically monitoring women under the age of 50 with onset of arthritis or else arthralgias associated with skin lesions, photosensitivity, Raynaud or systemic symptoms, especially if there are hematological alterations (cytopenias), or of the urine sediment, bearing SLE in mind in the differential diagnosis. Determining antinuclear antibodies and, where appropriate, specific antibodies, may be indicated in these women.

Diagnostic Confirmation

Laboratory Tests

Detection of Antinuclear Antibodies

What is the technique of choice to detect antinuclear antibodies?

A - As a general rule, the GDG does not recommend carrying out the antinuclear antibody detection test if there are not at least two clinical manifestations that suggest SLE (see Appendix 7 in the original guideline document).

A - The method of choice to detect antinuclear antibodies in the diagnostic process of SLE is the indirect immunofluorescence due to its high sensitivity.

B - The antinuclear antibody detection test by indirect immunofluorescence should preferably be carried out with human epithelial cellular (HEp-2) substrate.

A - If an enzyme-linked immunosorbent assay (ELISA) method is used to detect antinuclear antibodies, using a traditional technique or based on antigen microspheres with proven sensitivity similar or higher than indirect immunofluorescence, the positive result should also be confirmed via indirect immunofluorescence.

B - To establish the cut-off point and interpret the titre of antinuclear antibodies, the GDG recommends knowing the antinuclear antibodies levels of reference in the general population of application with no antinuclear antibody-related diseases.

A - Titres below 1:40 (<5 UI/ml) of antinuclear antibodies detected through indirect immunofluorescence should be considered as negative.

B - The GDG recommends considering as clinically relevant a titre of antinuclear antibodies detected by indirect immunofluorescence of 1:160 (≥20 UI/ml) or more in the Caucasian population of their context, and proceeding with the diagnostic confirmation cascade through the detection of specific anti-dsDNA and anti-extractable nuclear antigen (ENA) (mainly anti-Sm) antibodies.

A - The GDG recommends interpreting a positive result in the antinuclear antibody detection test in the patient's clinical context since, on its own, it does not establish the diagnosis of SLE at all.

C - In people with suggestive symptoms of SLE and antinuclear antibody detection test by indirect immunofluorescence with result persistently negative, the GDG suggests performing the antinuclear antibody detection via an ELISA technique that includes Ro (SSA) antigen reagents or the direct determination of anti-Ro (SSA).

B - The GDG recommends assessing the fluorescence pattern obtained in the antinuclear antibody detection test via indirect immunofluorescence to have useful additional information in the differential diagnosis of SLE with other systemic autoimmune diseases.

D - The GDG suggests that result report of the antinuclear antibody detection test includes the detection technique used, the positive dilution titre or the concentration of autoantibodies in UI/ml, together with the percentage of healthy individuals or individuals with no diseases associated with antinuclear

antibodies that present the same titre in the reference population, as well as the intensity and the nuclear, cytoplasmic and/or mitotic fluorescence patterns identified.

Diagnosis Confirmation

What is the validity of laboratory tests to confirm the diagnosis of systemic lupus erythematosus?

A - In people with symptoms or signs related to SLE and a positive antinuclear antibody (ANA) test, the GDG recommends determining specific high affinity immunoglobulin G (IgG) type anti-dsDNA antibodies and anti-Sm antibodies to confirm the diagnosis of SLE.

A - For the differential diagnosis of SLE with other connective tissue diseases in patients with positive ANA test, the GDG recommends determining anti-dsDNA antibodies via indirect immunofluorescence with *Crithidia luciliae* substrate.

A - SLE should be considered as first diagnostic option in patients with suggestive symptoms, a positive ANA test and a high titre of anti-dsDNA antibodies.

B - For the differential diagnosis of SLE with other connective tissue diseases in patients with positive ANA test, the GDG recommends determining anti-Sm antibodies with immunodiffusion (ID), immunoblotting (IB), counter-immunoelectrophoresis (CIE), ELISA or multiple simultaneous immunoassays with antigen microspheres.

A - The GDG does not recommend determining anti-RNP antibodies with diagnostic purposes in people with symptoms that are suggestive of SLE.

B - In people with symptoms or signs related to SLE, a positive ANA test and negative high affinity specific anti-dsDNA, anti-Sm and anti-nucleosome antibodies, determining specific anti-protein ribosomal P antibodies could be useful to diagnose SLE.

C - The GDG does not recommend determining anti-Ro and anti-La antibodies in order to diagnose SLE, unless there is an absence of other autoantibodies in people with suggestive symptoms.

C - The GDG recommends determining anti-histone antibodies only when people are suspected of having drug-induced SLE.

Diagnostic and Classification Criteria

What are the classification criteria for systemic lupus erythematosus? Should the new classification criteria proposed by the Systemic Lupus International Collaborating Clinics (SLICC) 2012 group be used as diagnostic criteria?

GCP - The GDG recommends basing the diagnosis of SLE on expert clinical opinion, combining suggestive clinical characteristics with serological confirmation.

GCP - The classification criteria should not be used with a diagnostic purpose; however, the SLICC classification criteria may provide useful guidance for the diagnosis.

B - The GDG recommends using the SLE classification criteria of the American College of Rheumatology (ACR) 1982-1997 and/or those of the SLICC 2012 to select homogeneous patients in clinical research and epidemiological studies.

Initial Evaluation Tests After Diagnosis

After confirming the diagnosis, what tests should be carried out to make an initial evaluation of any patient with systemic lupus erythematosus?

B - For the initial evaluation of patients diagnosed with SLE, the GDG recommends quantifying the different specific antibodies as activity markers and disease prognosis.

A - The GDG does not recommend the isolated use of anti-dsDNA antibodies to diagnose a flare of SLE.

C - The GDG recommends the joint assessment of the anti-dsDNA antibodies titre and the C3 and C4 complement levels as support to assess activity.

A - The GDG does not recommend the isolated determination or monitoring of anti-Sm or anti-RNP antibody levels to evaluate the global activity or risk of nephropathy of SLE.

B - The GDG does not recommend determining anti-ribosomal P antibodies as prognostic markers of neuropsychiatric episodes or of general activity of SLE, or in the initial assessment of patients diagnosed with SLE or during its evolution.

B - The GDG recommends determining anti-Ro and anti-La antibodies in all women with SLE before planning pregnancy or as soon as an unplanned pregnancy is acknowledged.

C - Due to its thrombosis and obstetric complication predictive value, the GDG suggests the periodic combined determination of antiphospholipid (anticardiolipin, lupus anticoagulant and anti-β2-glycoprotein I) antibodies in order to determine their persistence (if positive) or their positivitation with the course of the diseases (if negative).

B - The GDG does not recommend using the erythrocyte sedimentation rate as an SLE activity marker.

C - The GDG suggests carrying out urine sediment, protein/creatinine ratio in an early morning urine sample, proteinuria in 24-hour urine and serum creatinine, both at the time of diagnosis of SLE and during successive medical visits, to predict the presence and evolution of lupus nephropathy.

D - The GDG suggests performing complete routine blood tests to evaluate the existence of anemia, leucopoenia, lymphocytopenia and thrombocytopenia, both at the time of diagnosis of SLE and during successive medical visits.

General Management of Systemic Lupus Erythematosus

Monitoring

Clinical Monitoring Protocol and Complementary Tests

> What is the most recommendable clinical monitoring protocol for people with systemic lupus erythematosus?
> What complementary tests should be carried out on people with systemic lupus erythematosus, and how often, in monitoring and control consultations? Which are the most effective and cost-effective disease activity biomarkers for monitoring systemic lupus erythematosus? Should the 25 (OH) vitamin D levels be monitored as a systemic lupus erythematosus activity marker?

GCP - The GDG suggests performing a comprehensive, clinical and analytical assessment at the time the diagnosis of SLE is confirmed.

GCP - In the monitoring protocol of patients with SLE, the GDG suggests monitoring the activity of the disease, organ damage, comorbidities (including the presence of vascular risk factors) and the possible toxicity of the pharmacological treatment. To this end, the clinical interview, physical examination, blood pressure testing will be used, as well as basic analytical determinations that will include complete blood test, biochemical analysis with renal profile and urine analysis, complement and determination of anti-dsDNA antibodies.

GCP - In patients with active SLE, the monitoring intervals should be adapted to the clinical situation and they are, therefore, variable.

GCP - If the disease is in clinical and analytical remission, the GDG suggests monitoring every six to twelve months, depending on the disease evolution time and the treatment intensity.

C - In clinical quiescent patients with maintained activity analytical criteria, the GDG suggests closer monitoring, every three to four months, at least during the first years.

D - The GDG suggests periodically determining the levels of 25 (OH) vitamin D in SLE patients, especially

in the presence of osteoporotic fracture risk factors.

D - The GDG suggests the regular use of activity biomarkers such as levels of C3 and C4 and of anti-dsDNA in SLE patients, above all in those with renal involvement.

Disease Assessment Tools

Are the available standardized tools effective to assess the disease in clinical practice? Should they be used in normal clinical practice?

GCP - SLE patients require the highest standardized and objective monitoring of their disease as possible, so the GDG suggests the use of validated instruments to quantify the degree of activity, accumulated damage and quality of life.

Predictive Factors of Flare or Increase in Disease Activity

What are the analytical or biological markers that can predict a lupus flare or which factors have been associated with an increase in activity of systemic lupus erythematosus?

B - When following-up SLE patients, the GDG recommends using periodic determinations of C3, C4 and anti-dsDNA as predictors of active disease.

C - Although anti-C1q and antinucleosome antibodies are probably more sensitive and specific as lupus nephritis markers, the current lack of standardization advises against their routine use for this purpose.

General Therapeutic Approach

Therapeutic Objectives

What are the therapeutic objectives in people with systemic lupus erythematosus?

B - As the main therapeutic objective in SLE patients, the GDG recommends establishing the control of perceived or verifiable clinical lupus activity, avoiding secondary irreversible damage both to the disease itself (particularly renal and neurological damage, and cardiovascular events) and to its treatment, above all glucocorticoids (osteonecrosis, osteoporotic fractures, diabetes mellitus, cataracts, etc.), minimizing the impact on the patients' quality of life and survival.

B - The GDG recommends minimizing the risk of infections.

Treatment Indications

Non-biological Immunosuppressive Treatments

What non-biological immunosuppressive treatments are effective in extrarenal lupus?

B - The GDG recommends intravenous cyclophosphamide as first immunosuppressive drug in the treatment of SLE and of severe non-renal manifestations.

A - The GDG recommends methotrexate as first immunosuppressive drug in the treatment of nonrenal SLE with moderate activity, especially in those cases with cutaneous and joint manifestations.

GCP - As an alternative, the GDG suggests using other immunosuppressive drugs such as azathioprine (AZA), cyclosporine A, leflunomide or mycophenolate for the treatment of non-renal SLE.

Antimalarial Drugs

Is the use of antimalarial drugs indicated in all people with systemic lupus erythematosus? What is the effectiveness, cost-effectiveness and safety of these drugs in preventing flares? Have they got other additional beneficial effects that may justify their generalized use?

B - The GDG recommends using antimalarial drugs as the basic treatment for all SLE patients who have no contraindications for its administration.

B - The GDG recommends maintaining indefinite treatment with antimalarial drugs due to their effects on activity, damage, thrombosis, infections and long-term survival.

B - For its greater safety, the GDG recommends hydroxychloroquine instead of chloroquine as the antimalarial drug of choice.

D - The GDG suggests combining anti-malarial treatment with quinacrine and hydroxychloroquine in patients with refractory lupus activity, especially cutaneous, as this may produce synergic effects.

D - In patients with retinal toxicity caused by antimalarial drugs, the GDG suggests replacing hydroxychloroquine or chloroquine by quinacrine.

D - The GDG suggests active monitoring of retinal toxicity in patients treated with hydroxychloroquine or chloroquine.

D - The GDG suggests at least a baseline eye examination during the first year of treatment, and every year after the 5th year of treatment, although the control should be started earlier in patients with maculopathy of another origin or with additional risk factors.

D - The GDG suggests including at least one of the most sensitive techniques: spectral domain optical coherence tomography (SD-OCT), retinal autofluorescence or mutifocal electroretinogram, together with automated visual field 10-2.

Glucocorticoids

What is the recommended dose of glucocorticoids to keep the disease controlled with an assumable risk of adverse effects?

B - The GDG suggests not exceeding a dose of 30 mg/day of prednisone in the treatment of patients with lupus nephritis. However, the dose should be personalized.

GCP - In general, the GDG recommends not exceeding a dose of 30 mg/day of prednisone in other SLE manifestations. However, the dose should be individually assessed for each patient.

B - In serious flares, the GDG recommends coadjuvant treatment with methylprednisolone pulses.

C - The GDG suggests a rapid reduction of glucocorticoid doses (prednisone) in order to reach 5 mg/day, within six months at the very latest, trying to complete withdrawal as soon as possible.

B - If necessary in maintenance treatment, the GDG recommends that the prednisone dose does not exceed 5 mg/day.

GCP - The GDG suggests the use of methylprednisolone pulses below 1000 mg, although a specific dose cannot be recommended.

Biological Therapies

Which biological therapies are effective and safe in people with systemic lupus erythematosus?

A - The GDG recommends belimumab treatment for people with active SLE who have not responded to standard treatment and whose activity is not fundamentally due to renal or neurological activity.

B - The GDG suggests considering as candidates to belimumab treatment those people with active SLE not responding to a treatment for at least three months that includes antimalarial drugs, prednisone and at least one immunosuppressive drug at adequate dose. They also suggest considering as candidates to belimumab treatment those who need prednisone at a dose of 7.5 mg/day or more to maintain the remission, despite antimalarial drugs and at least one immunosuppressive drug, or contraindication for the use of clinically indicated immunosuppressive drugs for toxicity.

C - The GDG suggests administering rituximab in patients with severe renal, neurological or hematological activity who do not respond to first line immunosuppressive treatment.

GCP - Nowadays, there is no approved indication for the use of other biological agents in SLE. However, in certain situations where usual therapeutic measures (including belimumab and rituximab) have failed or cannot be used, the use of any one of the following agents could be considered: infliximab (in refractory arthritis and nephritis), etanercept (arthritis and serositis), abatacept (especially in arthritis) and tocilizumab (in patients with bad control of their clinical activity).

Immunoglobulins

What is the effectiveness and safety of immunoglobulins in treating systemic lupus erythematosus?

D - The use of intravenous immunoglobulins would be justified in severe immune life-threatening thrombocytopenia with active bleeding or when surgical intervention or hemorrhagic risk procedure is required.

D - The GDG suggests taking the necessary measures to reduce the toxicity risk: adequate infusion rate, avoiding products with high saccharose content, ruling out immunoglobulin A deficiency and carefully considering the risk-benefit balance. They suggest considering the use of thromboprophylaxis with heparin if thrombosis risk factors exist, guaranteeing adequate hydration. Likewise, in patients with associated renal failure risk factors, they suggest watching over the renal function during the days following the infusion.

GCP - Intravenous immunoglobulins could also be used in patients with high activity whose major organs are compromised in the presence of or suspected severe infection that contraindicates or substantially limits immunosuppressive treatment.

GCP - The GDG suggests administering the dose of intravenous immunoglobulins of 0.4 g/kg/day for five consecutive days. However, lower doses (for example, 0.5 g/kg one day) may also be effective, except in the case of thrombocytopenia.

GCP - The GDG does not recommend the use of intravenous immunoglobulins as maintenance treatment in any of the manifestations of SLE, as there are other therapeutic alternatives with more consolidated effectiveness and lower cost.

Adverse Effects and Monitoring Guidelines for Immunosuppressive and Biological Treatments

What are the complications and adverse effects of the most usual biological and immunosuppressive treatments of systemic lupus erythematosus? Which are the most advisable monitoring guidelines?

B - To monitor hematological and hepatic toxicity of immunosuppressive drugs, the GDG recommends carrying out complete blood tests and hepatic biochemical analyses at intervals of one to three months.

B - In patients treated with cyclophosphamide, the GDG recommends active surveillance of bladder cancer through a urine analysis in order to detect microhematuria. This surveillance should not cease after stopping the treatment.

D - The GDG recommends determining the activity of the thiopurine methyltransferase enzyme or its polymorphisms before starting the treatment with AZA.

Indication for Therapeutic Aphaeresis

What is the effectiveness and safety of therapeutic aphaeresis in treating systemic lupus erythematosus?

A - The GDG does not recommend plasmapheresis as first or second line treatment in SLE patients, either for global activity or in patients with nephritis.

C - In severe cases that are refractory to other therapies, the GDG suggests considering the use of plasmapheresis in an individualized manner.

Prevention of Disease Reactivation

Which measures are effective to prevent the reactivation of systemic lupus erythematosus?

A - The GDG recommends prolonged treatment with antimalarial drugs, to prevent reactivations of SLE, even during pregnancy.

A - Due to the unfavorable balance between the beneficial effect observed and the potential toxicity associated with excess of treatment with glucocorticoids, the GDG does not recommend the preventive administration of prednisone to patients with serological activity without associated clinical manifestations.

B - The GDG does not recommend that patients with clinically quiescent and serologically active SLE receive immunosuppressive treatment to prevent flares beyond their basic treatment or the remission maintenance treatment of lupus nephritis.

C - Although the GDG does not recommend vitamin D supplements with the sole objective of preventing activity flares, they do suggest correcting the vitamin D deficiency due to its effects on the bone mass and asthenia, not ruling out a beneficial effect in the control of lupus activity.

C - In addition to its harmful impact on other aspects of the disease and on global health, the GDG suggests avoiding smoking due to its possible effect on lupus activity, especially at cutaneous level.

Treatment of Associated Asthenia

Which therapeutic options are efficient to help people with fatigue associated with systemic lupus erythematosus?

B - The GDG recommends gradual sessions of aerobic physical exercise at home, controlled by a health professional (walking, static cycling, swimming), in people with stable SLE, due to its global improvement effect on several self-perceived measures by SLE patients.

B - Psycho-educational support should be offered to SLE patients to improve their knowledge and understanding of the disease, restructuring beliefs, improving coping and social support.

GCP - The GDG does not recommend vitamin D supplements in patients with fatigue and normal levels of 25 (OH) vitamin D.

GCP - Despite the effectiveness-related data derived from the randomized controlled trials (RCTs), the GDG does not recommend the administration of belimumab with the sole objective of improving fatigue.

Lifestyle Measures

Which lifestyle-related measures should be advised for patients with systemic lupus erythematosus?

GCP - The GDG recommends adopting active measures in order to help give up smoking in all SLE patients. This objective is especially important, not just because of the effect that smoking has on the activity of the disease and quality of life, but also because of its causal association with the increase in risk of cardiovascular disease, infection and cancer.

B - The GDG recommends promoting regular physical exercise in patients with stable SLE with low to moderate disease activity.

C - The GDG suggests avoiding being overweight and a sedentary lifestyle in all SLE patients.

C - The GDG suggests recommending a diet that is low in saturated fats and rich in omega-3 fatty acids for SLE patients.

Photoprotection

Is photoprotection indicated in all patients with SLE? Which photoprotection measures are effective?

A - The GDG recommends that the regular use of broad spectrum photoprotectors with high solar photoprotection index should be applied in adequate quantity (2 mg/cm^2), evenly over all the areas exposed to the sun, between 15 and 30 minutes before exposure and reapplied every two hours and/or

after immersion and perspiration.

GCP - The GDG suggests systematically informing and educating SLE patients, particularly those with cutaneous lupus and who have photosensitivity, about the photoprotection measures and the importance of their use to control their disease better and to avoid the appearance of other symptoms.

Educational Programs

Are structured nursing-based educational programs addressed to people with SLE effective?

C - The GDG suggests to perform structured educational programs addressed to SLE patients and provided by nursing professionals.

Management of Specific Clinical Manifestations

Lupus Nephritis

Indication for Renal Biopsy

What are the criteria for recommending a renal biopsy?

B - The GDG recommends performing a renal biopsy on all SLE patients who present confirmed proteinuria ≥0.5 g/day, particularly in the presence of active sediment and/or isolated renal insufficiency without alternative explanation.

C - The renal histopathological study should also inform of the class, degree of activity, chronicity, and presence of vascular and interstitial lesions.

C - The GDG does not recommend the routine repetition of renal biopsies, which would be limited to refractory patient or patients with renal relapse when it is considered that the result may determine a therapeutic change.

Therapeutic Objectives

What are the specific therapeutic objectives?

D - The main therapeutic objective for lupus nephritis (LN) are:

- Preserving the renal function in the long term
- Preventing relapses
- Avoiding secondary adverse effects of the treatment
- Improving survival and health-related quality of life (HRQoL)

C - To increase the probabilities of remission, the GDG recommends companion therapy with angiotensin converting enzyme inhibitors, or angiotensin receptor blockers for a good blood pressure control and to reduce proteinuria.

Refractoriness

Which circumstances define a lupus nephritis as refractory to treatment?

D - The GDG suggests considering as refractory those patients who do not reach at least partial remission after six months' treatment.

D - In patients with refractory lupus nephritis the GDG suggests, as a first measure, ensuring correct therapeutic compliance and verifying that the renal lesions are reversible.

D - In patients with nephritis who are refractory to treatment with cyclophosphamide or mycophenolate, the GDG suggests changing to another first-line drug (mycophenolate or cyclophosphamide).

D - In cases of refractory nephritis without satisfactory response to the change in first line treatment (cyclophosphamide and mycophenolate), the GDG suggests using rituximab, anticalcineurinics, Ig,

belimumab or drug combinations.

Induction Treatment

Induction Treatment of Proliferative Lupus Nephritis

> What should be the induction treatment of proliferative lupus nephritis?
> Under what conditions would induction treatment with mycophenolate afford advantages over other drugs?

A - The GDG recommends to all patients with proliferative lupus nephritis to be treated with immunosuppressive drugs in addition to corticosteroid therapy.

A - The recommended therapeutic strategy should include a response induction phase and a maintenance phase of this response with lower drug doses.

A - The immunosuppressive drug of choice recommended for the induction phase of a first flare of LN is cyclophosphamide in pulse therapy or oral mycophenolate.

A - The GDG does not recommend azathioprine for induction treatment.

C - In Hispanic patients from Latin America or African Americans, the GDG suggests administering mycophenolate instead of cyclophosphamide.

A - The recommended dose of intravenous cyclophosphamide for induction is 0.5 g/2 weeks (three months) or 0.75-1 g/m^2/month (six months).

B - The recommended dose of mycophenolate mofetil for induction is 2-3 g/day or the equivalent in sodium mycophenolate.

C - In women over 30 years of age or with a risk of ovarian insufficiency, the GDG suggests using minimum doses of cyclophosphamide (according to Eurolupus Nephritis Trial [ELNT] standard), or choosing mycophenolate both for induction and maintenance.

C - In women of childbearing age who have received cyclophosphamide reaching an accumulated dose greater than 8 g (or 5 g in women over 30), the GDG suggests mycophenolate (or azathioprine) as drug of first choice for maintenance in the current episode, and as induction and maintenance in successive episodes.

GCP - The GDG suggests pulse therapy with methylprednisolone in the most severe cases (nephrotic syndrome and/or renal insufficiency), with nephritic syndromes and/or renal insufficiency and as oral prednisone saver.

C - As a rule, the GDG suggests starting with oral prednisone doses no greater than 30 mg/day.

C - The reduction rate of prednisone should be fast up to doses of ≤5 mg/day, recommending reaching 5 mg/day after around three months and never after six months.

GCP - The GDG suggests pulse therapy with cyclophosphamide instead of mycophenolate in cases where therapy non-compliance is suspected.

C - The GDG suggests anticalcineurin therapy as alternative induction treatment, supervising the levels of the drug reached to reduce the risk of nephrotoxicity.

Induction Treatment of Lupus Nephritis with Renal Insufficiency

What induction treatment in lupus nephritis with renal insufficiency should be administered?

C - Both in cases of mild-moderate acute renal insufficiency (creatinine clearance > 30 ml/min/1.73m^2) and severe renal insufficiency (creatinine clearance < 30ml/min/1.73m^2), the GDG suggests using cyclophosphamide or mycophenolate mofetil (MMF) as induction immunosuppressive treatment.

GCP - The GDG suggests adapting the dose of cyclophosphamide in patients with renal insufficiency according to the estimated glomerular filtration and in patients receiving renal replacement treatment with dialysis.

GCP - The GDG suggests corticoid pulse therapy in all cases of LN with acute renal insufficiency unless it is contraindicated.

D - In LN lesions associated with ANCA+ necrotizing glomerulonephritis, the GDG suggests induction treatment with cyclophosphamide (CPM).

Maintenance Treatment

Maintenance Treatment of Proliferative Lupus Nephritis

What is the immunosuppressive maintenance treatment for proliferative lupus nephritis?

A - The GDG recommends oral mycophenolate or azathioprine for maintenance therapy of proliferative LN.

B - As an alternative to these, the GDG suggests intravenous cyclophosphamide in quarterly pulses or cyclosporine A.

Suspension of Maintenance Treatment

When and how should a maintenance treatment be discontinued?

B - The GDG recommends prolonging this maintenance treatment for two to three years at least.

C - The GDG suggests that in cases where the complete discontinuance of the maintenance immunosuppressive treatment is proposed, this should not be done before a clinical-analytical quiescence period of less than twelve months.

GCP - In patients with frequent relapses without any justifiable cause, or with risk factors for renal relapse, the GDG suggests prolonging the maintenance treatment for at least five years.

C - The GDG suggests that the total suspension of the maintenance immunosuppressive treatment should be slow and progressive.

C - The GDG suggests maintaining treatment with hydroxychloroquine for a long period, provided that it has no contraindications or side effects.

Immunosuppressive Treatment for Type V Lupus Nephritis

What should be the immunosuppressive therapeutic strategy of first choice for type V LN?

A - The GDG recommends immunosuppressive treatment in all patients with membranous lupus nephritis.

GCP - As in other types of nephritis, the GDG suggests not initially exceeding 30 mg/day of prednisone and then reducing it as soon as possible to 5 mg/day.

B - In induction treatment for patients with lupus nephritis class V LN and nephrotic proteinuria, the GDG recommends MMF and glucocorticoids as the treatment of choice. As an alternative and with the same induction efficacy although with more adverse effects, they recommend cyclophosphamide in intravenous pulses.

A/B - For maintenance regimens in patients with membranous LN, the GDG recommends treatment with mycophenolate (A) or azathioprine (B).

B - The GDG recommends using anticalcineurinics in membranous LN when seeking alternative drugs to mycophenolate or cyclophosphamide.

GCP - The GDG suggests combined therapy with mycophenolate and anticalcineurinics if complete remission is not achieved or if significant proteinuria persists.

C - The GDG suggests using rituximab associated with mycophenolate and methyl-prednisolone pulses when avoiding oral glucocorticoids is considered to be especially pertinent.

Haematological Manifestations

Immunosuppressive Treatment

First-line Treatment for Severe Cytopenias

What is the immunosuppressive first-line treatment for severe cytopenia?

D - The GDG suggests corticosteroid therapy as first-line immunosuppressive treatment for severe cytopenias of SLE.

GCP - Although oral prednisone is considered first-line treatment for immune cytopenias, there are no data supporting the use of higher doses over lower doses. The GDG suggests using intravenous pulses of methyl-prednisolone and the association of immunosuppressants, which would permit the initial use of lower daily doses of prednisone and quickly reducing to doses no more than 5 mg/day.

GCP - The GDG suggests oral treatment with dexamethasone at high doses (40 mg/day for four days), either combined with rituximab or not, as an alternative regimen that achieves a similar remission rate with a probably faster and longer-lasting response in idiopathic cytopenias.

Treatment of Thrombocytopenia

When should thrombocytopenia be treated?

GCP - In thrombocytopenia, the decision to start treatment is mainly based on the presence of bleeding manifestations and, on certain occasions, on a platelet count less than 20-30x10^9/L.

GCP - Patients with platelet counts between 20-30 and 50x10^9/L and a stable course, without hemorrhagic complications, are not candidates to receive treatment, except for those who present a hemorrhage or are going to undergo surgery or an invasive procedure.

GCP - The GDG suggests treatment with platelet counts of more than 50x10^9/L to be reserved for patients with a high risk of bleeding.

GCP - Despite the fact that platelet transfusions may be necessary before potentially bleeding procedures in patients with severe thrombocytopenia (platelet counts <10–30x10^9/L), transfusion should be avoided as a general rule if an underlying immune mechanism is suspected.

Treatment with Thrombopoietic Agents

What are the indications of thrombopoietic agents?

GCP - The GDG suggests considering the temporary use of thrombopoietic agents only in selected patients with severe symptomatic thrombocytopenia who do not respond to the initial standard treatment.

Neuropsychiatric Lupus

Diagnosis of Neuropsychiatric Complications

Usefulness of Certain Autoantibodies

What is the usefulness of certain types of autoantibodies for diagnosing neuropsychiatric complications?

B - There is no determination of autoantibodies that enables a confirmation diagnosis of neuropsychiatric SLE (NP-SLE) to be made.

B - The diagnosis of neuropsychiatric SLE continues to be made by exclusion and is mainly clinical. However, determining autoantibodies in serum or in cerebrospinal fluid could support the clinical

presumption of neuropsychiatric SLE.

B - The GDG recommends determining anti-neuromyelitis (NMO) antibodies in the event of suspected neuromyelitis optic associated with SLE.

Imaging Techniques

Which are the imaging techniques of choice in the diagnostic process of neuropsychiatric complications of systemic lupus erythematosus?

A - The GDG recommends performing magnetic resonance imaging (MRI) to patients with acute NP-SLE involving the central nervous system, mainly as a differential diagnosis tool, especially when neurological focality appears.

A - The GDG recommends MRI using T2 sequences in order to increase sensitivity.

C - If no explanation to the patient's symptoms is found after the evaluation with the recommended first line techniques, the GDG suggests using other magnetic resonance modalities or other types of imaging techniques such as the single-photon emission computed tomography (SPECT).

C - The GDG suggests using diffusion-weighted magnetic resonance or angio-MR to identify the etiology of lesions detected in traditional MR, and also in the case of suspected ischemic origin, in order to establish whether they are acute.

Indication for Neuropsychological Tests

Should neuropsychological tests be performed in all patients with suspected neuropsychiatric systemic lupus erythematosus?

B - The GDG recommends using structured interviews for the neuropsychological assessment of SLE patients.

C - The GDG suggests using the battery of neuropsychological tests proposed by the American College of Rheumatology (ACR) to assess neuropsychiatric manifestations of SLE, especially in cases of cognitive impairment.

C - The GDG suggests using validated neuropsychological tests validated in Spanish to monitor the neuropsychiatric outcomes of the progression of SLE, as well as to assess the effects of the interventions applied.

Indication for High Intensity Immunosuppressants

When are high-intensity immunosuppressive drugs indicated in patients with neuropsychiatric lupus?

D - The GDG suggests restricting treatment with glucocorticoids and/or immunosuppressants for neuropsychiatric SLE to those syndromes that express an underlying inflammatory process (organic brain syndrome, aseptic meningitis, myelitis, cranial or peripheral neuropathies, and psychosis) after excluding other causes not related to SLE.

A - The GDG recommends considering cyclophosphamide as immunosuppressive first-line treatment for severe neuropsychiatric SLE.

C - In patients with neuropsychiatric SLE in whom the use of cyclophosphamide is contraindicated, the GDG suggests using mycophenolate as an alternative.

C - Rituximab may be used as second-line in patients with neuropsychiatric SLE that are refractory to intravenous cyclophosphamide.

Lupus Arthritis

Evaluation Tools

Should a standardized tool be used to assess the state of arthritis? If so, which would be the most advisable?

GCP - The GDG suggests using the disease activity score (DAS-28) index to assess the state of arthritis in SLE patients only in those cases with arthritis of more than six weeks evolution.

Treatment

Which treatments are efficient and safe for lupus arthritis?

A - Methotrexate and anti-malarial drugs are the medications of choice in the case of joint manifestations of SLE.

C - There is little evidence about the use of other drugs for the specific treatment of lupus arthritis. The concrete indication for each one of them will depend therefore on the accompanying symptoms, the potential toxicity (including the possibility of pregnancy) and economic considerations.

GCP - The GDG recommends hydroxychloroquine with or without low doses of glucocorticoids (or pulses of 125 to 250 mg of methylprednisolone) in patients with: inflammatory arthralgias, intermittent arthritis or arthritis of less than six weeks evolution.

GCP - Patients who do not respond to the treatment, requiring doses of prednisone (or equivalent) over 5 mg with symptoms that last for more than six weeks or in cases where erosions or deformities appear, should be treated as chronic patients. The following regimens are recommended to treat chronic arthritis:

> Methotrexate as drug of choice
> If a satisfactory response is not obtained at full and subcutaneous doses within three months, add (or change) to another synthetic disease-modifying drug (leflunomide, azathioprine, cyclosporine A or mycophenolate), bearing in mind the other manifestations of SLE and the toxicity of each synthetic disease-modifying drug.
> If there is no response in three months, the GDG recommends adding biological therapy, more specifically, belimumab. If remission is not achieved within six months, rituximab, abatacept, etanercept, tocilizumab or other biological disease-modifying drugs could be used, although, unlike belimumab, none of them are released for use in SLE.

Mucocutaneous Manifestations

Cutaneous Lupus Evaluation Tools

Should a standardized tool be used to evaluate the stage of the disease? If so, which would be the most appropriate?

GCP - In patients in whom there is a prevalence of skin impairment, the GDG suggests using a standardized cutaneous activity index.

D - The GDG suggest using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) to assess the activity, damage and evolution of skin lesions in SLE patients.

Topical Treatment

What is the effectiveness, safety and cost-effectiveness of topical therapies in treating systemic lupus erythematosus with cutaneous manifestations? In which situations would they be indicated?

GCP - In cutaneous lupus, the GDG suggests the initial use of high-potency topical glucocorticoids.

GCP - In refractory cases, the GDG suggests using topical treatments with calcineurin inhibitors (tacrolimus or pimecrolimus).

Antiphospholipid Syndrome

Antiphospholipid Antibodies

What types and combinations of antiphospholipid antibodies increase the risk of thrombosis in people with systemic lupus erythematosus?

C - The GDG recommends determining antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies [aCL] and anti beta2-glucoprotein-I [β2-GPI]) on a regular basis as thrombotic risk markers in SLE patients.

Prevention and Treatment of Thrombotic Complications

What preventive and treatment measures should be taken for thrombotic complications in people with systemic lupus erythematosus and antiphospholipid antibodies?

C - The GDG suggests the use of hydroxychloroquine to reduce the risk of thrombosis in SLE patients, especially in those with antiphospholipid antibodies.

C - In SLE patients and high-risk antiphospholipid antibodies profile (presence of lupus anticoagulant, alone or combined with aCL or persistently positive aCL at medium-high titles or triple positivity), the GDG suggests treatment with low-dose aspirin to reduce the risk of thrombosis.

B - In patients with SLE and antiphospholipid syndrome with venous thrombosis, the GDG recommends anticoagulation with a target international normalized ratio (INR) 2.0-3.0.

C - In patients with SLE and antiphospholipid syndrome with arterial thrombosis, the GDG suggests anticoagulation with a target INR >3.0 or combining anticoagulants with INR 2.0-3.0 + low-dose aspirin.

C - In patients with SLE, antiphospholipid syndrome and thrombotic episodes, the GDG suggests indefinite anticoagulation.

GCP - The GDG suggests early identification and strict control of vascular risk factors in patients with SLE and antiphospholipid syndrome.

Sexual and Reproductive Health

Pregnancy

Planning Pregnancy

How would pregnancy be planned in women with systemic lupus erythematosus in order to maximize success possibilities?

D - The GDG suggests planning the pregnancy, including a preconception consultation, so that the gestation takes place in a clinical situation that minimizes the risks for the fetus and for the mother. If it has not been planned, they suggest assessing the patient as soon as the pregnancy has been acknowledged.

B - In the pre-gestation consultation the GDG recommends estimating the maternal risk profile based on the lupus activity, the extent to which the organs are affected, the autoantibody profile and the treatment received.

GCP - In the preconception consultation, the GDG suggests adjusting the treatment, substituting the medications that are contraindicated during pregnancy with others that are safe.

C - In planned pregnancies, the positivity or negativity of antiphospholipid and anti-Ro antibodies should be known in order to plan the monitoring of specific complications (heart block, placental insufficiency, preeclampsia).

GCP - The GDG suggests postponing pregnancy after a lupus flare until at least six months after remission, especially if the flare has affected vital organs.

B - The GDG recommends advising against pregnancy in women with SLE with pulmonary hypertension or with severe organ damage (kidney, heart or lung) due to serious risk for the lives of mother and foetus.

Monitoring Pregnancy

What specific monitoring should be carried out and how often in pregnant patients with SLE?

C - The GDG suggests multidisciplinary management of pregnant woman with SLE by the obstetrician and the specialist in autoimmune diseases, with the participation of other specialists if considered necessary.

GCP - From the medical viewpoint, the GDG suggests making one visit during the first trimester, every four to six weeks until week 26 of gestation, and every two weeks from week 27 until birth. This is subject to modifications according to obstetric and medical criteria.

GCP - During each visit, the GDG suggests monitoring the weight, blood pressure and the presence of proteinuria, especially in women with risk of LN and/or preeclampsia.

GCP - The GDG suggests determining C3 and C4 to monitor lupus activity, even though their levels are altered by the actual pregnancy.

GCP - The GDG does not recommend repeatedly determining antinuclear antibodies, anti-ENA or antiphospholipid antibodies.

GCP - The GDG suggests requesting anti-DNA in agreement with the clinically suspected flare.

GCP - The GDG recommends performing a series of ultrasound examinations similar to the following, always subject to the obstetrician's criterion:

> Week 8-9: Pregnancy confirmation ultrasound.
> Week 12: Ultrasound for triple screening of chromosomopathies. During this week, a first Doppler study of uterine arteries may be carried out in order to estimate the probability of preeclampsia in women at risk (those who test positive to antiphospholipid antibodies, have a history of nephritis, preeclampsia and/or high blood pressure).
> Week 20: Malformation ultrasound. If the uterine artery Doppler has not been carried out during week 12 or it was abnormal, the GDG recommends carrying it out this week.
> Week 24: The uterine artery Doppler can be repeated for the last time if it was abnormal, to see if has become normalized. If not, the pathology is considered as definite.
> Starting in week 24, growth ultrasounds and umbilical Doppler according to the obstetrician's criterion.

GCP - When the pregnant woman has positive anti-Ro and/or anti-La antibodies, the GDG suggests regular monitoring the fetal heart calculating the ultrasound PR interval between week 16 and 34, always in agreement with the criteria of the obstetrician and of the specialist in fetal cardiology.

Treatment with Antimalarial Drugs

Should antimalarial drugs be maintained if a pregnancy occurs? Which would be the drug of choice?

B - The GDG recommends maintaining hydroxychloroquine during pregnancy.

GCP - As hydroxychloroquine is safer during the pregnancy and more studies have been performed than with chloroquine, the GDG suggests using it as the antimalarial drug of choice in this situation.

Prevention of Obstetric Complications in Patients with Antiphospholipid Antibodies

What preventive measures should be taken for obstetric complications in patients with antiphospholipid antibodies?

GCP - The GDG suggests that patients with obstetric antiphospholipid syndrome and a history of repeated early miscarriages (≤10 weeks) should be treated with aspirin, with or without associated heparin.

GCP - The GDG suggests that patients with obstetric antiphospholipid syndrome and a history of fetal death (>10 weeks) or severe preeclampsia with placental insufficiency should be treated with aspirin and heparin at prophylactic doses.

GCP - The GDG suggests that asymptomatic carriers of antiphospholipid antibodies should be treated with aspirin.

C - The GDG suggests starting with aspirin prior to conception.

GCP - Due to its availability in Spain and its convenience, the GDG suggests using low molecular weight heparin rather than unfractionated heparin.

A - The GDG does not recommend using intravenous immunoglobulin for treating obstetric manifestations of the antiphospholipid syndrome.

GCP - Prednisone at a dose of ≤10 mg/day until the 14th week can be used in refractory cases, although this measure is not risk-free.

Fertility and Contraception

Assisted Reproduction Techniques

Are assisted reproduction procedures safe and efficient in SLE? Is ovarian stimulation safe in women with SLE?

GCP - The GDG suggests carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting assisted reproduction procedures, including ovarian stimulation, programming them under controlled disease situation.

GCP - The GDG suggests administering prophylactic treatment with low molecular weight heparin in patients with positive antiphospholipid antibodies.

Contraception Methods

What contraception methods are safe in women with SLE?

GCP - Although the benefits of hormone contraception may be greater than the risks in many women with SLE, the GDG suggests carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting treatment with combined hormone contraceptives.

B - In women with positive antiphospholipid antibodies, the GDG recommends avoiding combined hormone contraceptives due to having a greater risk of suffering arterial and venous thrombotic phenomena.

B - Given their safety, the GDG recommends bearing in mind the use of the intrauterine device (IUD) (including devices with progestogens) or barrier methods, within more suitable contraceptive methods for women with SLE, especially for women for whom the use of estrogen contraceptives is contraindicated.

Comorbidity

Cardiovascular Risk

Cardiovascular Risk Level and Cardiovascular Risk Assessment

> Do people with SLE have a greater cardiovascular risk? Is this risk similar across the different ethnic groups?
> Should the cardiovascular risk be evaluated in people with SLE? How should this be done and how often?

GCP - The GDG suggests assessing the cardiovascular risk with the same frequency as recommended for other high cardiovascular risk diseases such as diabetes, using the instruments available for the general population until specific and validated instruments for SLE are available, and individualizing the estimation according to specific risk-increase associated factors of SLE.

Prevention of Cardiovascular Events

Is there evidence about specific cholesterol figure targets, or can we only transfer those recommended for other high cardiovascular risk pathologies such as diabetes?

GCP - The GDG recommends establishing the recommended cholesterol figures for people with increased cardiovascular risk as those desirable for SLE patients.

Indication for Aspirin

In which people with systemic lupus erythematosus is the use of aspirin indicated?

GCP - The GDG recommends treating SLE patients who persistently present medium to high values of antiphospholipid antibodies with low doses of aspirin for the primary prevention of thrombosis.

GCP - The GDG suggests treating SLE patients and previous cardiovascular disease with low doses of aspirin under the same terms as for the general population.

Indication for High Blood Pressure Drugs

Is there evidence that favors the use of certain high blood pressure drugs such as angiotensin blockers, in people with systemic lupus erythematosus?

D - In patients with nephritis with proteinuria, the GDG suggests the use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

C - In patients with lupus and high blood pressure, the GDG suggests the use of angiotensin converting enzyme inhibitors due to their possible added value in the primary prevention of renal impairment.

Infection

Latent Infection Screening

What should the latent infection screening protocol be for people with SLE (tuberculosis, hepatitis C virus [HCV], hepatitis B virus [HBV], cytomegalovirus, etc.)?

GCP - The GDG cannot give a general recommendation on the indication or periodicity of repeated assessments of latent infection due to the human immunodeficiency virus, HBV, HCV, and tuberculosis. Therefore these should be adapted to the clinical situation and the individual risk factors of each patient.

GCP - The GDG suggests examining all patients who are going to be submitted to immunosuppressive treatment for human immunodeficiency virus, HBV, HCV, and tuberculosis, above all when this treatment involves high doses of glucocorticoids or biological therapies, regardless of the existence of risk factors.

D - For patients whose first tuberculin skin test is negative, the GDG suggests carrying out a second test one week later to induce the immunological memory (*booster* effect) as false negatives are more frequent in the elderly and in immunosuppressed patients.

GCP - The tuberculin skin test is the test of choice to detect tuberculosis, taking into account its sensitivity in diagnosing tuberculosis in the standard cut-off point (5 mm). However, previous bacille Calmette-Guerin (BCG) vaccination and/or immunosuppression, could make the QFT-G a more reliable test for detecting latent infection.

Pneumococcal Vaccine

What is the safety and efficacy of a pneumococcal vaccine in people with SLE? Should this vaccine be administered to all patients?

GCP - The GDG suggests administering the pneumococcal vaccine to SLE patients.

GCP - The GDG suggests administering the pneumococcal vaccine, preferably, during a stable phase of the disease.

GCP - For pregnant women with SLE, the GDG suggests following the existing recommendations for

pregnant women in the general population, if any. If there are none, they suggest not vaccinating until there is available scientific evidence.

Cancer

What are the most frequent types of cancer in people with systemic lupus erythematosus? Should specific screening be carried out for this type of patients?

C - The GDG suggests maximizing early cancer detection measures in patients with long-lasting SLE, organ damage and/or hematological participation, especially in patients treated with high doses of cyclophosphamide.

D - The GDG suggests that SLE patients should undergo a cervical cancer screening program more frequently than recommended for the general population, especially in presence of associated risk factors such as the use of immunosuppressants, a history of four or more sexual partners and/or a history of prior infection by human papilloma virus (HPV) or dysplasia.

Osteoporosis

Indication of Bone Densitometry (BMD)

Should bone densitometry be carried out on all people with SLE? If so, how often?

D - Given the lack of evidence, the GDG does not recommend carrying out a BMD test on all SLE patients.

GCP - For the estimation of fracture risk, including BMD, the GDG suggests following the recommendations applied to the general population, with special diligence in case of additional risk factors such as chronic treatment with glucocorticoids or menopause.

Prevention of Steroid-induced Osteoporosis

Which measures should be taken to prevent steroid-induced osteoporosis in people with systemic lupus erythematosus?

B - The use of calcium in monotherapy is not recommended to prevent steroid-induced osteoporosis.

C - In order to reduce the risk of steroid-induce osteoporosis in SLE, the GDG suggests avoiding long-term sustained doses of prednisone >5 mg/day in SLE. If it is necessary, steroid-saving drugs such as immunosuppressants should be used.

GCP - The GDG suggests recommending an adequate diet, resistance exercises, periodic measurement of BMD if prednisone >5 mg/day or equivalent are used for ≥ two to three months, calcium and vitamin D supplements, and evaluation of the need for pharmacological prophylaxis of osteoporosis with antiresorptive therapy.

GCP - The GDG suggests following the generic clinical practice guidelines for treatment of steroid-induced osteoporosis.

Definitions

Scottish Intercollegiate Guidelines Network (SIGN) Levels of Evidence

1++	High-quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very little bias risk
1+	Well-performed meta-analyses, systematic reviews of clinical trials, or well-performed clinical trials with little bias risk
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high bias risk
2++	High-quality systematic reviews of case-control or cohort studies. Well conducted studies of case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, such as case reports and case series
4	Expert opinion

Note: The studies classified as 1- and 2- must not be used in the recommendations preparation process due to their high bias possibility.

SIGN Grades of Recommendation

A	At least one meta-analysis, systematic review or clinical trial rated as 1++ and directly applicable to the target population of the guidelines; or a volume of scientific evidence comprised of studies classified as 1+ and with great consistency between them
B	A volume of scientific evidence comprised of studies classified as 2++, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 1++ or 1+
C	A volume of scientific evidence comprised of studies classified as 2+, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 2++
D	Scientific evidence of level 3 or 4; or scientific evidence extrapolated from studies classified as 2+
Good Clinical Practice (GCP)*	Recommended practice based on clinical experience and consensus of the drafting team

*At times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general these cases are related to some aspects of the treatment that nobody would normally question and they are evaluated as points of "good clinical practice."

Level of Evidence Grades for Questions on Diagnosis

National Institute for Health and Care Excellence (NICE) Adaptation of the Levels of Evidence of the Oxford Centre for Evidence-based Medicine and the Centre for Reviews and Dissemination

Ia	Systematic review with homogeneous level 1 studies
Ib	Level 1 studies
II	Level 2 studies Systematic review of level studies
III	Level 3 studies Systematic review of level 3 studies
IV	Consensus, expert opinions without explicit critical evaluation
Level 1 studies	They meet: Blinded comparison with a valid (golden standard) comparator test Suitable range of patients
Level 2 studies	They only show one of these biases: Non-representative population (the sample does not reflect the population in which the test will be used) Comparison with unsuitable comparator ("gold standard") (the rest to be assessed is part of the gold standard or the result of the test affects the performance of the gold standard) Non-blinded comparison Case and controls studies
Level 3 studies	They meet two or more of the criteria stated for level 2 studies

Recommendation Grades for Questions on Diagnosis

Recommendation	Evidence
A	Ia or Ib
B	II
C	III
D	IV

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Systemic lupus erythematosus (SLE)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Dermatology

Family Practice

Hematology

Internal Medicine

Nephrology

Nursing

Rheumatology

Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To develop a clinical practice guideline (CPG) that will serve as an instrument to improve the comprehensive healthcare of systemic lupus erythematosus (SLE) patients, establishing systematically developed recommendations based on scientific evidence that will help professionals and patients to make decisions about the most appropriate healthcare, and to select the most adequate and efficient diagnostic or therapeutic options to address their health problem, integrating in a coordinated manner the different National Health Service (NHS) resources involved
- To develop a useful tool to standardize the diagnosis and treatment of SLE
- To reduce unjustified variability in clinical practice in the comprehensive healthcare of SLE, both in terms of its diagnostic aspects and its therapeutic management
- To foster a comprehensive and integrated healthcare for the person, relatives and environment with a multidisciplinary perspective
- To facilitate coordination both among the different specialists involved in caring for SLE patients and among the different healthcare levels, helping to advance in the integrated management of the disease
- To improve the clinical skills of the health professionals involved in the healthcare of SLE patients
- To provide useful information on the efficacy, safety and efficiency of the different diagnosis techniques and of the (specific and symptomatic) pharmacological and non-pharmacological therapeutic options
- To provide useful information so that the people affected, their relatives and/or caregivers, and the health professionals involved in SLE care can make more appropriate decisions
- To help to homogenize the language used by the different experts, thus facilitating communication
- To detect research needs and to establish recommendations for future research on SLE

Target Population

Adults with systemic lupus erythematosus (SLE) according to diagnostic criteria of expert physician, regardless of the onset age and severity

Note: The most frequent manifestations are considered, excluding the disease that is restricted to the skin (cutaneous lupus), and the disease with terminal renal insufficiency, in a situation of dialysis or kidney transplant. Likewise, all the situations of the disease are considered, whether it is active, in remission, clinically quiescent or serologically active, pregnant patients, etc., adapting the management recommendations to each one of the situations described.

Interventions and Practices Considered

1. Diagnosis of systemic lupus erythematosus (SLE)
    - Early detection
    - Diagnostic confirmation
2. General management of SLE
    - Monitoring
    - General therapeutic approach
    - Lifestyle measures
    - Photoprotection
    - Educational programs for patients
3. Management of specific clinical manifestations
    - Lupus nephritis
    - Hematological manifestations
    - Neuropsychiatric lupus

- Lupus arthritis
- Mucocutaneous manifestations
- Antiphospholipid antibodies

4. Management of sexual and reproductive health
    - Pregnancy
    - Fertility and contraception
5. Management of comorbidity
    - Cardiovascular risk
    - Infection
    - Cancer
    - Osteoporosis

Major Outcomes Considered

- Diagnostic detection and accuracy
- Treatment efficacy and safety
- Health-related quality of life (HRQoL)
- Disease progression
- Long-term survival
- Flares
- Risk of complications
- Remission

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The steps followed are listed below:

Formulation of clinical questions following the Patient/Intervention/Comparison/Outcome (PICO) format.
Bibliographic search in: Medline and PreMedline via OvidSP, EMBASE via Elsevier and Science Citation Index Expanded (SCI-EXPANDED) and the Social Science Citation Index (SSCI) via Web of Knowledge, The Cochrane Library, PsycINFO, Scopus, TripDatabase, Canadian Medical Association (CMA) Infobase, International Guidelines Library (GIN), National Guideline Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group, Institute for Clinical Systems Improvement (ICSI) and National Health and Medical Research Council (NHMRC). Timeline: from May to December 2013. Languages: English and Spanish. The first phase involved a preliminary search for CPGs and systematic reviews in the aforementioned databases. Identified CPGs and systematic reviews were assessed with the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II), evaluated according to the criteria of SIGN, respectively. These documents have been included as a secondary source of evidence to respond to some specific sections of the guideline due to their rigor and clarity. An extensive search for primary studies (randomised clinical trials [RCTs,] observational

studies, and diagnostic test studies) was carried out in a second stage. Later, to identify further possible relevant studies, the entire development group was consulted until April 2014, the deadline for the first draft of the CPG.

To incorporate the perspective, experience and interests of systemic lupus erythematosus (SLE) patients into the clinical practice guideline (CPG), specifically in the scope, objectives and formulation of questions, apart from the participation of patients in all the stages of the guide development process (participating in the development group, participating in the experts group and participating in the external reviewer group), a systematic review (SR) of the literature was carried out of both qualitative and quantitative studies focused on identifying the impact of SLE on the lives of people with the disease and their environment, their experiences and needs for information and support. Furthermore, to complete this information, the perception of patients in the context of Spain was explored by means of a Delphi type three-round consultation carried out with the collaboration of Spanish Lupus Patients Federation (FELUPUS). Both the SR and the patient consultation have also allowed identifying those needs of patients that had not been sufficiently studied, in order to transfer them to the researchers interested in SLE.

The methodology used to prepare this CPG is included in the *Methodology Manual for Drafting CPGs in the National Health System (NHS)* (see the "Availability of Companion Documents" field).

Number of Source Documents

Refer to the Methodological Material document (see the "Availability of Companion Documents" field) for a breakdown of the studies identified and included for each clinical question.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Scottish Intercollegiate Guidelines Network (SIGN) Levels of Evidence

1++	High-quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very little bias risk
1+	Well-performed meta-analyses, systematic reviews of clinical trials, or well-performed clinical trials with little bias risk
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high bias risk
2++	High-quality systematic reviews of case-control or cohort studies. Well conducted studies of case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, such as case reports and case series
4	Expert opinion

Note: The studies classified as 1- and 2- must not be used in the recommendations preparation process due to their high bias possibility.

Level of Evidence Grades for Questions on Diagnosis

National Institute for Health and Care Excellence (NICE) Adaptation of the Levels of Evidence of the Oxford Centre for Evidence-based Medicine and the Centre for Reviews and Dissemination

Ia	Systematic review with homogeneous level 1 studies
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II	Level 2 studies Systematic review of level studies
III	Level 3 studies Systematic review of level 3 studies
IV	Consensus, expert opinions without explicit critical evaluation
Level 1 studies	They meet: Blinded comparison with a valid (golden standard) comparator test Suitable range of patients
Level 2 studies	They only show one of these biases: Non-representative population (the sample does not reflect the population in which the test will be used) Comparison with unsuitable comparator ("gold standard") (the rest to be assessed is part of the gold standard or the result of the test affects the performance of the gold standard) Non-blinded comparison Case and controls studies
Level 3 studies	They meet two or more of the criteria stated for level 2 studies

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The steps followed are listed below:

Quality assessment of the studies and summary of evidence for each question following Scottish Intercollegiate Guidelines Network (SIGN) recommendations. As suggested by the Spanish National Health System (SNHS) clinical practice guideline (CPG) development manual for diagnostic test studies, the Oxford Evidence-Based Medicine Centre system has been used for the diagnosis questions.
The determination of the evidence levels and the formulation of recommendations was based on SIGN methodology (see the "Rating Scheme for the Strength of the Evidence" field).

The methodology used to prepare this CPG is included in the *Methodology Manual for Drafting CPGs in the National Health System (NHS)* (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The steps followed are listed below:

Establishment of the clinical practice guideline (CPG) development group, made up of primary care physicians, medical specialists in rheumatology, internal medicine, nephrology, haematology,

dermatology, immunology and clinical pharmacy, nursing staff attached to a hospital rheumatology unit, specialists in methodology and a representative from the federation of systemic lupus erythematosus (SLE) associations of relatives and patients. The development group has been managed by a clinical and methodological coordination team.

To determine the strength of each one of the formulated recommendations, the development group has considered not only the level of evidence available but also the equilibrium between desirable and undesirable consequences of carrying out the recommendation. The good clinical practice recommendations have been formulated and agreed by consensus following a transparent methodology with a face-to-face meeting of the development group and a subsequent series of successive consultation rounds with a panel of experts. Depending on the nature of the recommendations, different groups of experts were formed (10-13 professionals) with members of the development group and the group of collaborating experts, representing the different medical and health specialities involved. The consultation was carried out individually and by means of the successive interaction of an online questionnaire supported by the mean results from the previous round, in order to generate convergence of opinions, following a modified Delphi methodology. The good clinical practice recommendations proposed by the development group were presented in the questionnaire, and the panel had to assess the appropriateness of each one of them (the relationship between benefit and harm) on a scale from 1 to 9, where 1 meant that the recommendation was inappropriate and 9 that it was fully appropriate. An intermediate score of 5 meant that the harm and the beneficial effects were almost the same or that the expert was not able not give an opinion on the recommendation. Finally, it was decided to include only those recommendations with median values between 7 and 9, and with a percentage of panelists scoring within that range of 70% or more, after the first or the second round.

In order to promote and facilitate the shared decision-making (SDM) process between SLE patients/relatives and the health professionals, the CPG development group identified grade A and B recommendations which, under their judgment, were more sensitive to the values and preferences of the patients, and therefore, in which the SDM process should be favoured (refer to Annex 2 of the original guideline document).

The methodology used to prepare this CPG is included in the *Methodology Manual for Drafting CPGs in the National Health System (NHS)* (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Scottish Intercollegiate Guidelines Network (SIGN) Grades of Recommendation

A	At least one meta-analysis, systematic review or clinical trial rated as 1++ and directly applicable to the target population of the guidelines; or a volume of scientific evidence comprised of studies classified as 1+ and with great consistency between them
B	A volume of scientific evidence comprised of studies classified as 2++, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 1++ or 1+
C	A volume of scientific evidence comprised of studies classified as 2+, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 2++
D	Scientific evidence of level 3 or 4; or scientific evidence extrapolated from studies classified as 2+
Good Clinical Practice (GCP)*	Recommended practice based on clinical experience and consensus of the drafting team

*At times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general, these cases are related to some aspects of the treatment that nobody would normally question and they are evaluated as points of "good clinical practice".

Recommendation Grades for Questions on Diagnosis

Recommendation	Evidence
A	Ia or Ib
B	II
C	III
D	IV

Cost Analysis

The guideline developer reviewed published cost analyses.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The steps followed are listed below:

> The collaborating experts have participated in the formulation of questions, in the development of search strategies, in the clinical good practice recommendations consensus process, and in the review of the first draft of the clinical practice guideline (CPG).
> External reviewers have participated in the review of the second draft. The purpose of submitting the CPG to external review was to improve the overall quality, to ensure the appropriateness of recommendations, to disseminate the evidence, as well as to assess its applicability and feasibility. The methods used to carry out the external review were the use of the Word track changes tool and comments in the margin of the text, or an evaluation of the different sections of the CPG by means of a template.
> As the first step in the development process of this CPG, the different scientific societies involved were contacted (rheumatology, internal medicine, nephrology, hematology and haemotherapy, dermatology and venereology, neurology, primary care physicians, hospital pharmacy, primary care pharmacists, family and community medicine, nursing), agreeing on the representatives for the development group. They were also represented in the group of expert collaborators and the group of external reviewers.

The methodology used to prepare this CPG is included in the *Methodology Manual for Drafting CPGs in the National Health System (NHS)* (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline

Recommendations

Potential Benefits

- Improved treatment appropriateness
- Improved quality of life

Refer to the original guideline document for information about the benefits of specific interventions observed in the studies that were reviewed for this guideline.

Potential Harms

- False-positive and false-negative results of diagnostic tests
- Adverse effects of treatment

Refer to the original guideline document for information about the harms of specific interventions observed in the studies that were reviewed for this guideline.

Contraindications

Contraindications

Several documents contain expert recommendations with relation to planning pregnancies in women with systemic lupus erythematosus (SLE). In these recommendations, a series of contraindications for gestation are established, such as pulmonary hypertension or severe organ damage (kidney, heart or lung).

Qualifying Statements

Qualifying Statements

This clinical practice guideline (CPG) is an aid for decision making in health care. It is not mandatory, and it is not a substitute for the clinical judgement of healthcare personnel.

Implementation of the Guideline

Description of Implementation Strategy

Dissemination and Implementation Strategy

Clinical practice guidelines (CPGs) are useful to improve the quality of healthcare and outcomes in patients. The great challenge today is to achieve professionals' adherence to the recommendations of these guidelines. An implementation strategy, aimed at overcoming the existing barriers in the medium where it is going to be applied is therefore essential.

The CPG is comprised of two versions for health professionals: full and abridged. Both have information for patients. All the CPG versions are published in electronic format, available on the GuíaSalud Web site (www.guiasalud.es). The dissemination and implementation plan of the guideline on systemic lupus erythematosus (SLE) includes the following interventions:

Official presentation of the guideline by the health authorities to the media.
Presentation of the guideline to the directorates and sub-directorates for primary care and specialized care of the different health services.
Forwarding of e-mail to entities and resources to inform about the CPG, as well as to the professional groups involved (general practitioners and specialists in rheumatology, nephrology, hematology, internal medicine, immunology, dermatology, nurses, midwives) to facilitate dissemination.
Effective distribution aimed at the professional groups involved (specialists in rheumatology, nephrology, hematology, internal medicine, immunology, dermatology, nurses) to facilitate dissemination.
Dissemination of the guideline on electronic format on the Web sites of the Ministry of Health, Social Services and Equality, of GuíaSalud, of the Canary Island Health Service Assessment Service, and of the societies involved in the project.
Publication of the guideline in scientific magazines.
Presentation of the guideline at scientific activities (conferences, congresses, meetings).

Indicator Proposals

Measuring adherence to or implementation of the CPG recommendations by monitoring and/ or auditing can improve its use. The Appraisal of Guidelines Research and Evaluation (AGREE) II instrument manual includes the importance of developing indicators, where item 21 on the applicability dimension is the one that deals with this aspect. Consequently, a CPG should offer a list of clear and quantifiable quality indicators or criteria, which are derived from the key recommendations included in the guideline. The most well-known classification of indicators, and used in this guideline is the Donabedian classification, which groups them into: structure, process and results. To determine and evaluate compliance with the recommendations considered to be most important, the assessment of some process variables and most important clinical results is proposed.

The indicators proposed by the guideline development group are listed and described in Section 9 of the original guideline document. They are classified according to the clinical area, type of indicator, dimension of the quality they address and the healthcare level where they may be applied (primary care and/or specialized care). It is important to bear in mind that the indicators are a proposal and are only an approach. As they are quantitative measures, if they are obtained with certain regularity, the evolution can be analyzed in time (monitoring). The authors' purpose has not been to design a comprehensive and detailed assessment that entails using all the proposed indicators. On the contrary, the aim is to provide stakeholders and clinicians with a tool that may be useful in the specific design of the care assessment. The people responsible for assessing the impact of the CPG and for caring for patients should choose the most suitable information sources and most advisable period of time that each indicator refers to.

Refer to Section 9 of the original guideline document for proposed indicators.

Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Guideline Development Group of the Clinical Practice Guideline on Systemic Lupus Erythematosus. Clinical practice guideline on systemic lupus erythematosus. Madrid (Spain): Evaluation Service of the Canary Is. Health Service, GuiaSalud, Ministry of Health (Spain); 2015. 432 p. [854 references]

Adaptation

Not applicable: The guideline is not adapted from another source.

Date Released

2015

Guideline Developer(s)

Evaluation Service of the Canary Is. Health Service - National Government Agency [Non-U.S.]

GuiaSalud - National Government Agency [Non-U.S.]

Ministry of Health (Spain) - National Government Agency [Non-U.S.]

Guideline Developer Comment

Collaborating Scientific Societies

- Spanish Rheumatology Society (SER)
- Spanish Society of Internal Medicine (SEMI)
- Spanish Nephrology Society
- Spanish Society of Hematology and Haemotherapy
- Spanish Academy of Dermatology and Venereology
- Spanish Neurology Society (SEN)
- Spanish Society of Primary Health Care Physicians (SEMERGEN)
- Spanish Hospital Pharmacy Society (SEFH)

Spanish Society of Primary Health Care Pharmacists (SEFAP)
Spanish Society of Family and Community Medicine (SemFYC)
Spanish Nursing Scientific Society (SCELE)

Members of these societies have taken part as authors, expert collaborators and external reviewers of the clinical practice guideline (CPG).

Source(s) of Funding

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Guideline Committee

Guideline Development Group of the Clinical Practice Guideline on Systemic Lupus Erythematosus

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Financial Disclosures/Conflicts of Interest

All members of the Development Group, as well as those who participated in the expert collaboration and external review, made the declaration of interest appearing in Appendix 1 of the original guideline document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available in English and Spanish from the GuíaSalud Web site.

Availability of Companion Documents

The following are available:

Quick reference guides and summary versions are available in Spanish from the GuíaSalud Web site .

Clinical practice guideline on systemic lupus erythematosus. Methodological material. El Rosario (Spain): Evaluation Service of the Canary Islands Health Service (SESCS); 2015. 385 p. Available in Spanish from the GuíaSalud Web site .

Grupo de trabajo sobre GPC. Elaboración de guías de práctica clínica en el Sistema Nacional de Salud. Actualización del manual metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud - I+CS; 2016. Guías de práctica clínica en el SNS: I+CS, nº 2006/1. Available in Spanish from the GuíaSalud Web site .

The Spanish version of the guideline is also available via a mobile application from the GuíaSalud Web site .

Patient Resources

Patient information can be found in Appendix 12 of the original guideline document . A Spanish version is also available from the GuíaSalud Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on June 12, 2018. The information was verified by the guideline developer on June 26, 2018.

This NEATS assessment was completed by ECRI Institute on June 13, 2018. The information was verified by the guideline developer on June 26, 2018.

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